Supplementary materials of “The impact of the underlying risk in control group and effect measures in non-inferiority trials with time-to-event data: a simulation study” by Xuanqian Xie, Chenglin Ye, Nicholas Mitsakakis

**Appendix 1:** The relationship of the underlying risk and scale parameter of Weibull distribution

**Figure A1:** Underlying risk versus scale parameter (Lambda) of Weibull distribution



**Appendix 2:** SAS code of simulating survival data of the hypothetical trials

**%Macro** Non\_inferiority (HR=, N\_study=, N\_pt=, risk\_low=, Risk\_high=, t\_recruit\_max=, t\_censor\_adm\_min=, t\_censor\_adm\_max=);

data TE\_data;

/\*To simulate N trials \*/

do iter= **1** to &N\_study;

/\*Paramters for time to event data\*/

 Shape = **2**;

 T = **5**;

 Risk = &Risk\_low + (&Risk\_high - &Risk\_low)\* RAND('UNIFORM') ;

 risk\_round= round (Risk, **0.01**);

 Lambda = - (log(**1**-Risk) /(T\*\*Shape));

/\*Transform parameters for SAS Weibull function which is used different parameterization.\*/

 Scale\_0 = (**1**/Lambda)\*\*(**1**/Shape);

 Scale\_1 = (**1**/(Lambda\*&HR))\*\*(**1**/Shape);

/\*Paramters for time to random cencoring: exponential distribution, 10% in year 5\*/

 Shape\_cen = **1**;

 T\_cen = **5**;

 Lambda\_rdm\_cen = - (log(**1**-**0.1**)/(T\_cen\*\*Shape\_cen));

Scale\_cen = (**1**/Lambda\_rdm\_cen)\*\*(**1**/Shape\_cen);

/\*To simulate N patient for each trial\*/

 do i = **1** to &N\_pt; \* Number of “patients” simulated;

 t\_recruit = &t\_recruit\_max\* RAND('UNIFORM') ; \*recruitment period;

 t\_censor\_rdm = rand("WEIBULL", **1**, Scale\_cen); \*The time to censoring for radnom reasons;

 /\* \*hypothetical administrative censoring time ;\*/

 t\_censor\_adm = &t\_censor\_adm\_min + (&t\_censor\_adm\_max - &t\_censor\_adm\_min)\* RAND('UNIFORM') ;

 group = rand('BERN', **0.50**); \*equal number in two groups;

 if group= **0** then do;

 t\_event = rand("WEIBULL", shape, Scale\_0); \* time of event;

 end;

 if group= **1** then do;

 t\_event = rand("WEIBULL", shape, Scale\_1); \* time of event;

 end;

 censor\_t = min (t\_censor\_rdm, t\_censor\_adm - t\_recruit); /\*censoring time\*/

 time = min(t\_event, censor\_t); \* which came first?;

 Status = (t\_event lt censor\_t); \* time-to-Event before time-to-censoring;

 output;

 end;

 end;

run;

**%MEND**;

%***Non\_inferiority*** (HR=**1**, N\_study=**10000**, N\_pt=**600**, risk\_low=**0.2**, Risk\_high=**0.95**,t\_recruit\_max=**2**,t\_censor\_adm\_min=**5.75**, t\_censor\_adm\_max=**6.25**);

**Appendix 3:** Additional results of sensitivity analysis

**Table A1:** The probability of rejecting the null hypothesis – sample size of trial (true hazard ratio = 1)

| **Effect measure** | **Non-inferiority margin** | **Underlying risk in control group** |
| --- | --- | --- |
|  |  | < 10% | 10-25% | 25-75% | >75% |
| **Sample size of each hypothetical trial = 2,000** |
| **Hazard ratio** |  |  |  |  |  |
|  | HR= 1.2 | 0.157 | 0.364 | 0.747 | 0.917 |
|  | HR= 1.35 | 0.361 | 0.767 | 0.983 | 1.000 |
|  | HR= 1.5 | 0.578 | 0.943 | 0.998 | 1.000 |
| **DTKME** |  |  |  |  |  |
|  | DTKME = 2.5% | 0.542 | 0.250 | 0.198 | 0.282 |
|  | DTKME = 5% | 0.988 | 0.784 | 0.541 | 0.764 |
|  | DTKME = 10% | 1.000 | 1.000 | 0.981 | 1.000 |
|  | DTKME = 15% | 1.000 | 1.000 | 1.000 | 1.000 |
|  |  |  |  |  |  |
| **Sample size of each hypothetical = 10,000** |
| **Hazard ratio** |  |  |  |  |  |
|  | HR= 1.2 | 0.582 | 0.943 | 1.000 | 1.000 |
|  | HR= 1.35 | 0.940 | 1.000 | 1.000 | 1.000 |
|  | HR= 1.5 | 1.000 | 1.000 | 1.000 | 1.000 |
| **DTKME** |  |  |  |  |  |
|  | DTKME = 2.5% | 1.000 | 0.892 | 0.605 | 0.865 |
|  | DTKME = 5% | 1.000 | 1.000 | 0.996 | 1.000 |
|  | DTKME = 10% | 1.000 | 1.000 | 1.000 | 1.000 |
|  | DTKME = 15% | 1.000 | 1.000 | 1.000 | 1.000 |

Abbreviation: HR=Hazard ratio; DTKME=difference in two Kaplan–Meier estimators.

**Table A2:** The probability of rejecting the null hypothesis – shape parameter in Weibull distribution (true hazard ratio = 1)

| **Effect measure** | **Non-inferiority margin** | **Underlying risk in control group** |
| --- | --- | --- |
|  |  | < 10% | 10-25% | 25-75% | >75% |
| **Shape parameter = 0.5, hazard decreasing over time** |
| **Hazard ratio** |  |  |  |  |  |
|  | HR= 1.2 | 0.079 | 0.117 | 0.333 | 0.513 |
|  | HR= 1.35 | 0.211 | 0.302 | 0.703 | 0.926 |
|  | HR= 1.5 | 0.316 | 0.444 | 0.912 | 1.000 |
| **DTKME** |  |  |  |  |  |
|  | DTKME = 2.5% | 0.316 | 0.093 | 0.071 | 0.143 |
|  | DTKME = 5% | 0.724 | 0.302 | 0.214 | 0.439 |
|  | DTKME = 10% | 1.000 | 0.864 | 0.695 | 0.887 |
|  | DTKME = 15% | 1.000 | 0.994 | 0.947 | 0.996 |
|  |  |  |  |  |  |
| **Shape parameter = 1, constant hazard** |
| **Hazard ratio** |  |  |  |  |  |
|  | HR= 1.2 | 0.045 | 0.193 | 0.328 | 0.535 |
|  | HR= 1.35 | 0.134 | 0.310 | 0.718 | 0.916 |
|  | HR= 1.5 | 0.254 | 0.491 | 0.912 | 0.996 |
| **DTKME** |  |  |  |  |  |
|  | DTKME = 2.5% | 0.269 | 0.111 | 0.065 | 0.168 |
|  | DTKME = 5% | 0.597 | 0.368 | 0.211 | 0.385 |
|  | DTKME = 10% | 0.985 | 0.848 | 0.659 | 0.858 |
|  | DTKME = 15% | 1.000 | 0.982 | 0.938 | 1.000 |

Abbreviation: HR=Hazard ratio; DTKME=difference in two Kaplan–Meier estimators.

**Table A3:** The probability of rejecting the null hypothesis – hazard of censoring

| **Effect measure** | **Non-inferiority margin** | **Underlying risk in control group** |
| --- | --- | --- |
|  |  | < 10% | 10-25% | 25-75% | >75% |
| **No random censoring**  |
| **Hazard ratio** |  |  |  |  |  |
|  | HR= 1.2 | 0.096 | 0.121 | 0.357 | 0.561 |
|  | HR= 1.35 | 0.193 | 0.302 | 0.712 | 0.925 |
|  | HR= 1.5 | 0.277 | 0.511 | 0.923 | 1.000 |
| **DTKME** |  |  |  |  |  |
|  | DTKME = 2.5% | 0.241 | 0.099 | 0.081 | 0.178 |
|  | DTKME = 5% | 0.590 | 0.319 | 0.213 | 0.388 |
|  | DTKME = 10% | 0.988 | 0.813 | 0.647 | 0.883 |
|  | DTKME = 15% | 1.000 | 1.000 | 0.940 | 0.986 |
|  |  |  |  |  |  |
| **Constant hazard of censoring, λ=0.0446 of exponential distribution**  |
| **Hazard ratio** |  |  |  |  |  |
|  | HR= 1.2 | 0.067 | 0.163 | 0.277 | 0.450 |
|  | HR= 1.35 | 0.107 | 0.299 | 0.658 | 0.941 |
|  | HR= 1.5 | 0.213 | 0.490 | 0.881 | 1.000 |
| **DTKME** |  |  |  |  |  |
|  | DTKME = 2.5% | 0.187 | 0.143 | 0.074 | 0.113 |
|  | DTKME = 5% | 0.667 | 0.381 | 0.183 | 0.306 |
|  | DTKME = 10% | 0.973 | 0.857 | 0.592 | 0.829 |
|  | DTKME = 15% | 0.987 | 0.973 | 0.892 | 0.995 |
|  |  |  |  |  |  |
| **Constant hazard of censoring, λ=0.1386 of exponential distribution** |
| **Hazard ratio** |  |  |  |  |  |
|  | HR= 1.2 | 0.038 | 0.093 | 0.254 | 0.357 |
|  | HR= 1.35 | 0.090 | 0.236 | 0.552 | 0.824 |
|  | HR= 1.5 | 0.141 | 0.379 | 0.775 | 0.967 |
| **DTKME** |  |  |  |  |  |
|  | DTKME = 2.5% | 0.115 | 0.099 | 0.085 | 0.071 |
|  | DTKME = 5% | 0.436 | 0.205 | 0.142 | 0.200 |
|  | DTKME = 10% | 0.910 | 0.702 | 0.428 | 0.595 |
|  | DTKME = 15% | 1.000 | 0.944 | 0.777 | 0.914 |

Abbreviation: HR=Hazard ratio; DTKME=difference in two Kaplan–Meier estimators.